

d his

(FILE 'HOME' ENTERED AT 17:54:14 ON 18 OCT 2004)

FILE 'REGISTRY' ENTERED AT 17:54:26 ON 18 OCT 2004

E AMLODIPINE/CN

1 S E3

E ATORVASTATIN/CN

1 S E3

FILE 'CAPLUS' ENTERED AT 17:56:37 ON 18 OCT 2004

1747 S L1 OR AMLODIPINE OR PELMEC OR NORVASC

1584 S L2 OR ATORVASTATIN OR LIPITOR

19 S L3 (L) L4

0 S L5 NOT PY>=1999

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH' ENTERED AT 17:58:08 ON

18 OCT 2004

0 S L6

13364 S AMLODIPINE OR PELMEC OR NORVASC

10180 S ATORVASTATIN OR LIPITOR

107 S L8 (L) L9

0 S L10 NOT PY>=1999

FILE 'DRUGU, IMSRESEARCH' ENTERED AT 18:00:38 ON 18 OCT 2004

3 S L11

ANSWER 1 OF 3 DRUGU COPYRIGHT 2004 THE THOMSON CORP on STN
SESSION NUMBER: 1998-32025 DRUGU T E S
LE: Choosing the most appropriate treatment for stable angina.
Safety considerations.
HOR: Asirvatham S; Sebastian C; Thadani U
PORATE SOURCE: Univ.Oklahoma
ATION: Oklahoma City, Okla., USA
RCE: Drug Safety (19, No. 1, 25-44, 1998) 5 Tab. 142 Ref.
CODEN: DRSABE ISSN: 0114-5916
AIL. OF DOC.: Division of Cardiology, University of Oklahoma Health
Sciences Center, 920 SL Young, 5SP-300, Oklahoma City, OK
73190, U.S.A. (U.T.).
LANGUAGE: English
DOCUMENT TYPE: Journal
ELD AVAIL.: AB; LA; CT
LE SEGMENT: Literature
1998-32025 DRUGU T E S
The treatment of stable angina is reviewed with reference to safety
considerations. The pathophysiology, natural history and prognosis of
stable angina are discussed. Drug therapy for plaque stabilization,
prevention of MI and mortality reduction is discussed with reference to
aspirin, ticlopidine, lipid lowering therapy, estrogen supplementation,
ACE-inhibitors and antioxidants. Symptomatic treatment with nitrates,
beta-blockers and Ca²⁺ antagonists is considered. Guidelines for
choosing appropriate drug or combination therapy for stable angina are
given.
EX Aspirin reduces mortality and morbidity in patients with acute coronary
syndromes. Its main adverse effects are GI. It interacts with warfarin,
corticosteroids, NSAID, alcohol and uricosuric drugs. Ticlopidine is used
as an alternative to aspirin in patients with stable angina pectoris.
Drugs used to lower serum lipids include colestyramine, colestipol,
nicotinic acid, fluvastatin, lovastatin, simvastatin, gemfibrozil and
probucol. Colestipol and colestyramine interact with digoxin, warfarin
and phytomenadione. Mibefradil can interact with lovastatin or
simvastatin. Estrogen supplementation in postmenopausal women can reduce
the risk of coronary artery disease, but can increase the risk of breast
cancer, endometrial hyperplasia and thrombosis. ACE-inhibitors
(enalapril, fosinopril, ramipril, captopril, benazepril and quinapril)
may also be useful for the treatment of stable angina. Adverse effects
include cough, hypotension, renal effects, angioedema and hyperkalemia.
ACE-inhibitors interact with furosemide, hydralazine, indometacin and
aspirin. Antioxidants (tocopherol, beta-carotene and retinol) may
protect against coronary artery disease. Effort angina is treated with
isosorbide dinitrate, isosorbide mononitrate and nitroglycerol.
Beta-blockers (propranolol, metoprolol) can be used to reduce myocardial
ischemia. They interact with verapamil, lidocaine and phenytoin. Ca²⁺
antagonists (verapamil, nifedipine, **amlodipine**, felodipine,
diltiazem and mibefradil) are often used to treat angina pectoris. They
may interact with quinidine, digoxin, rifampicin, carbamazepine,
ciclosporin, **atorvastatin**, terfenadine, astemizole, cisapride
and cerivastatin. (E83)

2 ANSWER 2 OF 3 DRUGU COPYRIGHT 2004 THE THOMSON CORP on STN
SESSION NUMBER: 1998-29103 DRUGU P T S
FILE: Mibefradil, a pharmacologically distinct calcium antagonist.
THOR: Ernst M E; Kelly M W
PORATE SOURCE: Univ.Iowa
ATION: Iowa City, Iowa, USA
RCE: Pharmacotherapy (18, No. 3, 463-85, 1998) 4 Fig. 5 Tab. 100
Ref.
CODEN: PHPYDQ ISSN: 0277-0008
AIL. OF DOC.: College of Pharmacy, The University of Iowa, S411 Pharmacy
Building, Iowa City, IA 52242, U.S.A..
LANGUAGE: English
DOCUMENT TYPE: Journal
ELD AVAIL.: AB; LA; CT
LE SEGMENT: Literature

1998-29103 DRUGU P T S

The characteristics of mibefradil (MB, (1S,2S)-2-((3-(2-benzimidazolyl)propyl)methylamino)ethyl)-6-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2-naphthylmethoxyacetate HCl2) are reviewed, with reference to its chemistry, pharmacology, pharmacokinetics, pharmacodynamics, efficacy in animal models and patients with hypertension, chronic stable angina pectoris and heart failure, adverse events and drug interactions. Other Ca antagonists mentioned include diltiazem, verapamil, **amlodipine**, felodipine and nifedipine. Agents investigated for interactions with MB include terfenadine, astemizole, cisapride, lovastatin, simvastatin, **atorvastatin**, cerivastatin, pravastatin, digoxin, fluvastatin, quinidine, imipramine, desipramine, enalapril, atenolol, cimetidine, theophylline, warfarin and phenytoin.

EX MB is the prototype of a new class of Ca antagonists that selectively block T-type voltage-gated plasma membrane calcium channels in vascular smooth muscle. MB is structurally and pharmacologically different from traditional Ca antagonists such as diltiazem and verapamil. MB does not have negative inotropic effects at therapeutic concentrations and is not associated with reflex activation of neurohormonal and sympathetic systems. In patients with hypertension, MB at 50 and 100 mg/day reduces trough sitting diastolic and systolic B.P. Doses of over 100 mg/day do not increase efficacy, but were associated with a greater frequency of side-effects. MB has antiischemic properties resulting from dilation of coronary and peripheral vascular smooth muscle, and from a slight reduction in HR. In clinical studies of chronic stable angina pectoris, MB leads to dose-dependent increases in exercise duration and time to onset of angina. MB reduces the number and duration of ischemic events, the number of anginal episodes and nitroglycerol consumption. MB has a favorable pharmacokinetic profile, with a high trough:peak ratio (over 80%), good oral bioavailability and a long-elimination half-life. Dizziness, headache, leg edema and lightheadedness are frequently reported with MB. The most frequent EEG changes associated with MB are 1st-degree A.V. block and sinus bradycardia. In-vitro, MB inhibited cytochrome P450 1A2, 2D6 and 3A4 and should thus not be given with terfenadine, astemizole, cisapride, lovastatin, simvastatin, **atorvastatin** and cerivastatin. The dose of MB should be reduced when it is given with imipramine or desipramine. (E61/MB)

2 ANSWER 3 OF 3 DRUGU COPYRIGHT 2004 THE THOMSON CORP on STN

CESSION NUMBER: 1998-25850 DRUGU T P E S

TLE: Drug administration in patients with diabetes mellitus.
Safety considerations.

THOR: Gilbert R E; Cooper M E; Krum H

RPORATE SOURCE: Univ.Melbourne; Univ.Monash

CATION: Melbourne, Austr.

URCE: Drug Safety (18, No. 6, 441-55, 1998) 2 Tab. 96 Ref.

CODEN: DRSAE ISSN: 0114-5916

AIL. OF DOC.: Endocrinology Unit, Austin and Repatriation Medical Centre
(Austin Campus), Studley Road, Heidelberg, Victoria 3084,
Australia.

NGUAGE: English

CUMENT TYPE: Journal

ELD AVAIL.: AB; LA; CT

LE SEGMENT: Literature

1998-25850 DRUGU T P E S

The drugs used in patients with diabetes mellitus are reviewed, with emphasis on safety considerations. Areas covered in the review include the effect of diabetes mellitus on drug handling, drugs used to control hyperglycemia in these patients, including metformin, the sulfonylureas, newer agents such as troglitazone and acarbose and insulin and drugs used to treat diseases associated with diabetes mellitus included antihypertensives and lipid-lowering agents.

EX Drug dose adjustment is rarely required where diabetes mellitus is well controlled. In the context of poor metabolic control or in the presence of complications such as nephropathy, significant alterations in drug handling may occur. Rarely, metformin use may be complicated by lactic acidosis. Long-term metformin may impair the absorption of cyanocobalamin and folate. The sulfonylureas chlorpropamide and

glibenclamide have longer durations than glipizide, glicazide or tolbutamide. Other sulfonylureas include tolazamide and acetohexamide. Long-acting sulfonylureas are best avoided in patients at high risk of hypoglycemia. The latter may be potentiated by drug interactions with phenytoin, rifampicin, warfarin, phenylbutazone and salicylates. Sulfonylureas may also interact with antacids, histamine H2 antagonists, omeprazole, beta-blockers, steroids, ACE inhibitors, perhexiline, chloramphenicol, ciprofloxacin, clofibrate, diuretics, dicoumarol, fluconazole, ketoconazole, fluoxetine, phenelzine, isocarboxazid, tranylcypromine and oxyphenbutazone. Troglitazone may be associated with abnormalities in liver function in about 2% of patients. The adverse effects of acarbose tend to improve with continued therapy. Drugs used to treat diseases associated with diabetes mellitus include ACE inhibitors such as enalapril, Ca antagonists such as nisoldipine, fosinopril and **amlodipine**, beta-blockers such as carvedilol, diuretics, HMG CoA reductase inhibitors such as lovastatin, pravastatin, simvastatin, fluvastatin and **atorvastatin**, and the fibrate derivatives clofibrate, gemfibrozil, bezafibrate or fenofibrate. (E61/MB)

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

CN 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, monobenzenesulfonate (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Benzenesulfonic acid, compd. with 3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate (1:1)

OTHER NAMES:

CN (+)-3-Ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate monobenzenesulfonate

CN Amcard

CN Amdepin

CN Amdipin

CN Amlodin

CN Amlodipine benzenesulfonate

CN Amlodipine benzenesulfonate salt

CN Amlodipine besylate

CN Amlopin

CN Amlor

CN Amlosyn

CN Antacal

CN Calchek

CN Istin

CN Lowrac

CN Monopina

CN Norvas

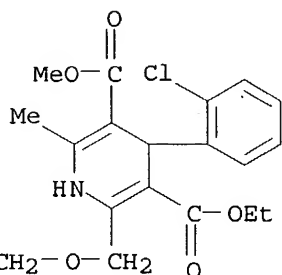
CN **Norvasc**

CN Norvask

CN Tensivask

CN UK 48340-26

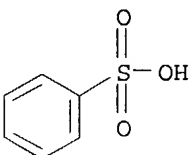
CM 1



H₂N-CH₂-CH₂-O-CH₂

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

CM 2



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT